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Transcriptomic insights into human brain evolution: acceleration, neutrality, heterochrony

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Primate brain transcriptome comparisons within the last 12 years have yielded interesting but contradictory observations on how the transcriptome evolves, and its adaptive role in human cognitive evolution. Since the human-chimpanzee common ancestor, the human prefrontal cortex transcriptome seems to have evolved more than that of the chimpanzee. But at the same time, most expression differences among species, especially those observed in adults, appear as consequences of neutral evolution at *cis*-regulatory sites. Adaptive expression changes in the human brain may be rare events involving timing shifts, or heterochrony, in specific neurodevelopmental processes. Disentangling adaptive and neutral expression changes, and associating these with human-specific features of the brain require improved methods, comparisons across more species, and further work on comparative development.

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Introduction

Humans are efficient cultural accumulators and niche constructors [1,2]. However, this is not because they are individually superior over other animals in every cognitive aspect. Chimpanzee performance in physical intelligence tests [3] or working memory tasks [4,5] appears comparable to infant or adult humans. The difference rather lies in human social intelligence and abilities, including spoken language, prosocial and cooperative behavior, and inclination to learn and teach [1,6•]. These characters, in turn, are associated with human-specific changes in brain development, anatomy, and physiology.

Comparative anatomical studies indicate that human and chimpanzee brain structure and developmental patterns closely resemble one another, relative to other primates (reviewed in [7–9]). Thus, most major characteristics of the human brain evolved in the great ape common ancestor. But species differences do exist, including three times more neurons and lower neuron density in the cortex, increased dendritic arbor, new connections, and prolonged development of the human brain relative to the chimpanzee brain (Table 1). The aim is, on the one hand, to predict the cognitive and behavioral consequences of these structural novelties; on the other, to identify the underlying human-specific genetic changes. The latter will inform on how human evolution unfolded, for example, whether it involved numerous genetic changes of small effect, or few with large effect. It can also allow partial reconstruction of human evolutionary history by comparison with extinct hominins with known genomes, such as Neanderthals and Denisovans (e.g. [10•,11,12]).

Evolutionary changes in brain structure, developmental timing, or neuronal physiology can arise from two types of effects. The first type is rather qualitative; it involves changes in protein activity through emergence of new genes, protein domains, or single amino acid changes. Between human and chimpanzee, coding differences are common (about two amino acids per ortholog), but most of these substitutions are predicted to be neutral [13]. Also, there exist very few human *de novo* genes [14,15]. The second type is relatively quantitative and involves expression changes, that is, changes in mRNA and protein abundance. These occur through *cis* effects (copy number, enhancer, promoter, UTR sequence changes) or *trans* effects (changes in transcription factor [TF], microRNA, DNA methyltransferase and chromatin modifier activity or post-translational modifications) [16].

Comparative developmental studies in animal models clearly demonstrate the role of gene expression changes, in the level, timing, location, or splicing pattern, as major contributors to the evolution of new forms and adaptive functions [17•,18]. Developmental expression changes are frequently driven by small alterations in *trans* effectors' coding or regulatory sequence, modifying gene expression networks and reorganizing existing modular processes (e.g. extension of progenitor mitotic activity).

Table 1

Anatomical, histological and molecular features of the human brain relative to those of chimpanzees.

A — Anatomy and connections
a. ~3 times larger volume; ~3 times more neurons; higher encephalization [105].
b. Higher proportion of neocortex, especially the prefrontal and temporal cortices; increased cerebellar connections; increased connections within the prefrontal cortex [8,105].
c. Slightly higher cortical folding (gyrification) in the neocortex, especially in the PFC [106].
d. Larger temporal cortex white matter [107].
e. Relative enlargement and increased left-right asymmetry in the Broca's area [108].
f. Expanded white-matter connection between frontal and temporal cortices, which could be related to language use [109].
g. Possible loss of a network hub in the medial PFC [110].
B — Cell types and histology
a. Higher glia to neuron ratio [38••].
b. Higher proportion of large spindle projection neurons in layer V (but little difference in pyrimidal or fusiform cells) [111].
c. Wider interneuronal spacing, or neuropil, in the PFC than in other cortical regions, indicating higher dendrite, spine, axon density [112,113] (a feature which develops after adolescence [114]).
d. Wider interneuronal spacing in the Broca's area [115].
e. Wider minicolumns and more interneuronal spacing on the left hemisphere [116].
f. Assymetry in interneuronal spacing in the left hemisphere [116].
g. Longer dendrites in cortical neurons [117]
h. Higher total number but lower density of von Economo neurons (spindle cells) [118].
C — Development and aging
a. Faster brain growth starting from 16 weeks of gestation [119] and continuing into infancy [120].
b. Faster PFC white matter volume growth during postnatal development [121].
c. Extended duration of cortical myelination [36].
d. Delayed peak of synapse numbers in PFC [64••] (but see [95]).
e. Relatively earlier initiation of white matter decay [122].
f. Prominent brain shrinkage at old age [123].
D — Physiology
a. Higher levels of resting-state brain activity in language areas [124].
b. Higher activity of metabolic pathways [22,30•,125,126].

Intuitively, developmental expression changes might have played similar roles in human brain evolution [19••]. Hence, once microarray technology became available, multiple groups moved to compare mRNA abundance between human and chimpanzee adult cortical regions and other tissues. The expectation was that a few genes would exhibit prominent activation shifts on the human lineage, and these could be readily associated with human-specific traits. On the contrary, the first studies found that hundreds to thousands of genes showed significant mRNA abundance differences between humans and chimpanzees [20,21••,22], most with ambiguous functional roles. Furthermore, many of these species differences were shared across brain regions with distinct functions [23] (reviewed in [24]).

Human acceleration?

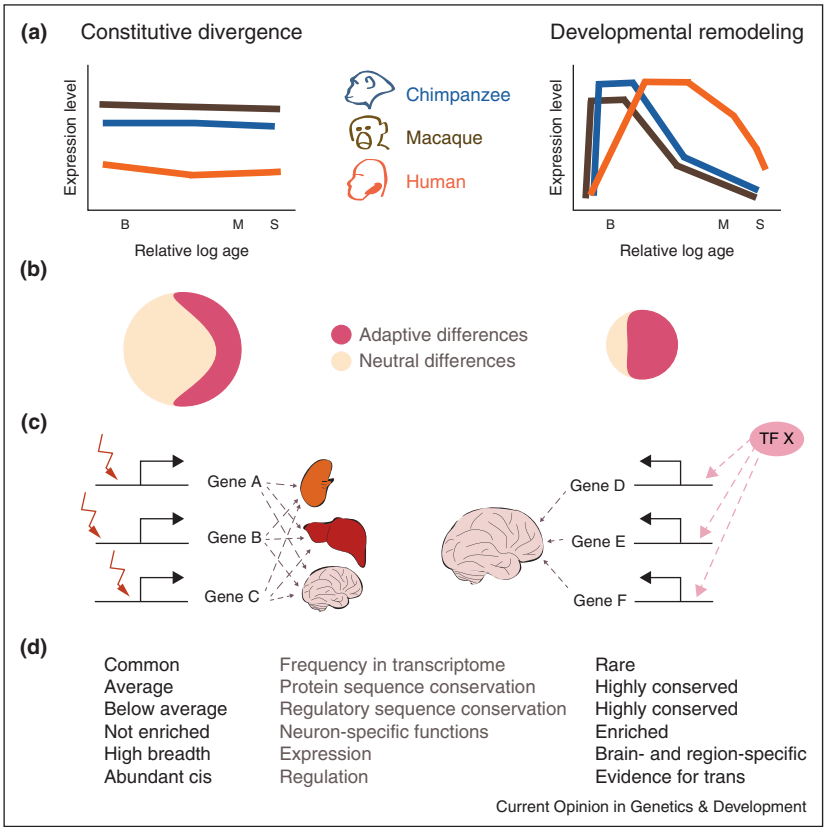
Despite this initial disappointment, some of the early studies found an excess of gene expression change on the human lineage, or human acceleration. One study detected five times more human-specific expression changes than chimpanzee-specific ones, and only in the brain, but not blood or liver [21••]. Another found dozens of genes with elevated expression only in humans, including genes with roles in synaptic plasticity (e.g. calcium/calmodulin-dependent protein kinase II alpha, *CAMK2A*, and carbonic anhydrase II, *CA2*) [20].

Human brain acceleration is intriguing, as the brain transcriptome is highly conserved compared to most other tissues, and brain-specific genes' coding sequences are under strong negative selection [25,26•]. Also notably, these studies had investigated expression levels in the prefrontal cortex (PFC), a region involved in high order, partly human-specific cognitive processes such as abstract thinking and planning [27]. An abundance of human-specific molecular changes in a highly conserved tissue with human-specific functions was suggestive of adaptive evolution. It supported the old notion that the human brain transcriptome divergence could explain human cognitive divergence [19••].

Subsequent work, however, revealed equivocal results. Some, using different brain regions [22] or technology [28], reported similar magnitude of change on the human- and chimpanzee lineages. Another found higher similarity between human and gorilla brain transcriptomes than with the chimpanzee, implying chimpanzee acceleration (although the effect here was not quantified) [26•].

Yet others reported human acceleration but in specific contexts. An investigation into metabolome and metabolite-related enzymes did find more adult human-specific changes in the PFC than chimpanzee-specific changes

Figure 1



Two types of transcriptome divergence, constitutive divergence (CD) and developmental remodeling (DR), are described in schematic diagrams, on the left and right panels, respectively. **(a)** Hypothetical examples of CD and DR as observed in comparative expression levels over age (B: birth, M: maturity, S: senescence; maturity is closer to senescence using log-transformed age models); **(b)** rough relative frequencies of CD and DR including the approximate hypothesized proportions of neutral versus adaptive differences in each; **(c)** the regulatory properties of CD and DR: *cis* and *trans* mechanisms predicted to be dominating each, and having high and low expression breadth, respectively; **(d)** a table contrasting their observed characteristics, in the categories listed in the middle column. Although CR is the predominant divergence type observed in the transcriptome, we suggest that DR might have played the main role in human cognitive evolution. Both hypotheses and data based on [34••].

[29]. But surprisingly, the skeletal muscle metabolome showed human acceleration even stronger than the PFC [30•]. Using comparative gene expression network analysis of correlated expression patterns between human, chimpanzee and macaque brains [31,32], one study identified more human-specific than chimpanzee-specific co-expression modules in the frontal pole, but not in caudate nucleus [33•]. Another study sorted human, chimpanzee and macaque brain expression differences into those involving developmental pattern differences (developmental remodeling), and those constitutive across postnatal development (i.e. same gene expression difference found both in newborns and in adults) (Figure 1) [34••]. Humans and chimpanzees showed similar levels of constitutive divergence, but humans showed higher intensity of developmental remodeling (see below).

One possibility is that human acceleration in the brain is caused by technical issues: difficulties in obtaining homologous brain structures, environmental differences, or microarray hybridization or RNA-sequencing read alignment artifacts could all create human-specific biases. In multiple studies reporting human transcriptome acceleration in PFC, other brain regions (e.g. visual cortex, caudate nucleus, cerebellum) exhibited little or no acceleration [30•,33•,34••], arguing against purely technical biases. Still, more heterogeneous tissue composition or expression of more recently duplicated genes in the PFC could create region-specific effects. This awaits future investigation.

The acceleration signal is clearly more pronounced in the PFC than other brain regions. Not only did the human PFC acquire new cognitive functions, but it also underwent dramatic enlargement and changes in developmental timing [35,36] (Table 1). In fact, structural expansion and developmental timing changes themselves generate shifts in tissue composition, which translate into differences in cell type proportions within the

tissue. Expression changes may then reflect differences in cell type ratios, as shown in blood [37]. Indeed, glia/neuron ratio in the human adult PFC appears significantly higher than in chimpanzees [38••] and glia-specific energy metabolism genes (e.g. *CA2*) appear up-regulated in human [20]. Acceleration of the adult human brain transcriptome may thus be largely a consequence of earlier developmental shifts and tissue composition changes, rather than cell-autonomous changes.

Neutral divergence?

Human and non-human primate comparisons yielded another set of stimulating observations, that (a) genes showing high mRNA level divergence between species also show high diversity within species (which are probably genes under weaker negative selection); (b) gene expression differences tend to accumulate linearly over evolutionary time [22,39••], revealing a phylogenetic signal similar to accumulating neutral mutations [40] (but might taper off in the long run [26•,41•]); (c) genes showing the highest expression divergence also evolve at faster, relaxed rates in their coding sequence [25]; (d) the major type of brain transcriptome divergence, constitutive divergence, involves broadly expressed genes without brain-specific functions and with below-average sequence conservation; and these appear driven by *cis* effects [34••] (Figure 1).

These observations raise the possibility that transcriptome evolution is largely shaped by a combination of negative selection and neutral genetic drift. The bulk of detected expression divergence is caused by accumulating neutral *cis* mutations [39••,42], instead of positive selection. The idea of neutral transcriptome evolution was initially contested [43,44] but today it seems better recognized (e.g. [45]). Still, alternative models do exist (see below).

Neutral *cis*-driven divergence may affect other aspects of gene regulation. Cerebellar splicing differences between humans and other primates appeared largely *cis*-driven and showed limited tissue-specificity [46]; tissue-specificity in splicing was particularly lower than observed using mRNA levels [47]. Another study on A-to-I RNA editing differences between humans and other primates in PFC and cerebellum, found more RNA editing differences between species than between brain regions or developmental stages [48]. This implies rapid evolution, and possibly, relaxed constraints. Also interestingly, genes linked to hundreds of human PFC-specific H3K4me3 gains, a marker of open chromatin, showed no specific association with neuronal activity; nearly 1/4 of these genes had DNA methylation signatures in the direction of higher gene activity in sperm [49]. Thus, not just constitutive mRNA level differences, but also a significant portion of splicing, RNA editing and histone modification differences between humans and other species' brains appear to be ubiquitously expressed, not brain-specific. Fast evolution and broad expression breadth imply that many differences are driven by neutral *cis* mutations and represent phenotypically silent molecular changes.

Phenotypic silence can also arise from expression differences canceling each other out or being buffered. In adult primate brain transcriptome data, numerous small down-regulations, perhaps representing slightly deleterious *cis* fixations, could be compensated by rare large up-regulations, which could be adaptive [50,51]. Meanwhile, many mRNA level species differences may not be translated, as shown in human and chimpanzee cell lines [52•].

Functional and adaptive divergence?

How to then identify mRNA abundance changes with phenotypic effect and adaptive roles in human cognitive evolution? In comparisons involving few species, the classical ANOVA approach will be insufficient to rule out neutrality (Box 1). Additional information is required. If multiple functionally-related genes show expression change in the same direction (e.g. up-regulation), this is an indication of a pathway being altered, with likely phenotypic consequence. Such co-divergence could be caused by a single *trans* change (e.g. up-regulation of a shared TF), itself driven by environmental differences between species, adaptive evolution, or genetic drift. Co-divergence could also be caused by multiple *cis* changes in the *same* direction, implying positive selection (as demonstrated in yeast [53,54]). In primates, however, linking expression divergence to causal *cis* changes has difficulties.

One alternative approach for identifying putative functional expression differences involves searching for lineage-specific expression shifts in highly conserved processes. For this, one can compare human expression levels to numerous diverse species (e.g. [55]) (Box 1). One can also compare humans' and other primates' transcriptomes during development, when even small changes produce large phenotypic outcomes [9,17•,56]. As argued above, functional gene expression changes observed in adults either reflect cell-autonomous changes in physiology (e.g. higher aerobic metabolism) or shifts in cell type composition or cellular anatomy (e.g. higher glia ratios or longer dendrites). As the latter is driven by modular changes in conserved developmental pathways, it makes double sense to study ontogenesis.

A role for heterochrony

The few studies on comparative primate postnatal brain development transcriptomics published to date, made interesting points. In the PFC and cerebellum, 50–70% of the expressed genes show changes in mRNA abundance during postnatal development and aging, with the

Box 1 Models for identifying differential expression

A major goal in comparative expression studies is to identify genes with differing expression between species, which may be caused by adaptative evolution. Earlier microarray-based comparative expression analyses generally relied on ANOVA-style analyses to detect genes with high expression variance between species, as compared to within species [42,43,78–82] (reviewed in [83]). The ANOVA approach effectively identifies genes with different mean expression levels between species, given the degree of expression variance within species.

However, applying ANOVA assumes independence between species, implicitly ignoring different divergence times. As more species are included in a study, it becomes important to consider differences in expression between species in the context of their varying phylogenetic relationships [84]. For example, using ANOVA, a neutral expression shift on a long phylogenetic branch may be misinterpreted as an adaptive shift, while a relatively small, but biologically meaningful expression shift on a short branch may be overlooked.

A number of researchers have considered phylogenetic correlations by modeling expression evolution as an Ornstein-Uhlenbeck (OU) process [41•,85–87]. An OU process can be thought of as a random walk with some pull towards a particular value. In the expression evolution analogy, an OU process models expression level drift over evolutionary time with some stabilizing selection towards an optimal value, as is common in quantitative comparative studies [88]. If that stabilizing selection is reduced to zero, the OU process models pure drift. Adaptive shifts in expression can be modeled using branch-specific optimal expression levels. Using these different evolutionary regimes, specific tests can be performed querying expression level shifts, stabilizing selection, and drift (but see [89]). With these advantages, OU processes are emerging as a convenient and relevant framework for investigation of adaptive expression hypotheses [26•,41•,55,89,90,91].

OU models have been applied to comparative time series expression data, treating each time point independently, to elucidate the evolution of development [90]. Further sophistication of these methods is required for a unified expression model over evolutionary and developmental time. Additionally, variance within species must be considered in phylogenetic methods [89,91]. As these studies illuminate mechanisms of expression level evolution (for example, mutational effect on expression level [92]), models must be flexible enough to incorporate this changing information.

most rapid changes taking place in newborns [34••,57,58]. 30–50% of these genes, as well as genes not showing developmental regulation in the brain, display constitutive expression divergence (Figure 1) [34••]. Meanwhile, developmental trajectories (i.e. the timing of mRNA abundance changes) are generally conserved: if a human gene is up-regulated during postnatal development, >80% of the time, its macaque ortholog is also up-regulated [58]. Trajectories are still, but less conserved during aging [58] (in contrast to [59]).

Developmental trajectory differences, or remodeling, are rare and appear as shifts in timing, instead of novel trajectories. Most timing differences scale with life-history differences, reflecting human altriciality and ~1.5 times slower maturation relative to chimpanzees [60,61]. Interestingly, timing shifts are not uniform across genes: some genes' expression profiles reveal heterochrony (greater delay or acceleration relative to maturation rate difference between species [62,63••]), with bias towards human delays [57].

Heterochronic expression differences themselves have a number of characteristics [34••]: (a) they occur as coordinated changes across hundreds of neural function-associated genes; (b) in the PFC, they happen 5 times more in the human lineage than the chimpanzee lineage, but less so in the cerebellum; (c) they are brain region-specific; (d) intriguingly, genes showing the strongest remodeling effects are the most conserved in their protein and regulatory sequences, arguing against major *cis* contribution to remodeling; (e) TF and microRNA show more human-specific remodeling than their putative targets. Also, several of these human-specific microRNA expression patterns were linked to expression changes in their targets *in vitro*, providing an explanation for co-divergence across hundreds of genes [34••].

A follow-up study on these expression profiles found evidence for an exceptionally delayed/extended period of high synaptic density in the human PFC [64••] (Box 2). This heterochronic phenotype, driven by *trans* regulators, could enhance learning and cultural transmission in humans [1,61].

Extended synaptogenesis is yet the only transcriptomic example of human heterochrony possibly linked to phenotypic differences. Meanwhile, many other evolutionary changes in the human brain could involve similar heterochronic, *trans*-regulated changes in core neurodevelopmental modules: for example, shifts in the duration and rate of symmetric and asymmetric progenitor divisions, enhanced signaling for dendritic arborization and gliogenesis, or prolonged myelination (Table 1). Comparative genomic studies have already identified candidate human-specific genetic changes causing heterochrony: for example, loss of a conserved enhancer, which could increase neuron numbers by restricting a mitotic inhibitor (growth arrest and DNA-damage-inducible gamma, *GADD45G*) deployed in brain development [65]; or gain of a truncated SLIT-ROBO rho GTPase activating protein 2 (*SRGAP2*) copy, which could promote spine density in the human neocortex by restricting *SRGAP2A*, a limiting agent in spine development [66•].

Neurodevelopmental genes, TFs and microRNAs interestingly pop up in various genome scans for human-specific changes, either in non-coding intergenic RNA [65,67,68], in recent segmental duplications [69], among recently evolved primate [70] or human [14,71] genes, among genes with divergent promoters in humans [72], or modern human-specific substitutions not shared with Neanderthals [10]. This implies liberal introduction of novel regulatory and coding sequence variants into neurodevelopmental networks and major remodeling of

Box 2 Heterochrony and extended synaptogenesis in humans

A recent study on postnatal brain development in humans, chimpanzees and macaques demonstrated how transcriptome analyses can inform about phenotypic divergence [64••]. In this dataset, genes involved in synaptogenesis and synaptic elimination in the PFC showed significantly delayed changes in humans. Neither synaptic expression in cerebellum, nor other processes such as myelination or axonogenesis in PFC, showed comparable delay (but see [36]). Metabolomic, proteomic and electron microscopy data from the same samples similarly indicated a difference in synaptic density between human newborns and other species [64••].

In fact, delayed synaptic maturation in human PFC relative to macaque had been known, but whether this was human-specific, or hominoid-specific, had remained unclear [93]. According to this study, peak density of synapses in PFC (later removed by synaptic pruning [94]) occurs shortly after birth in macaque and chimpanzee, but in humans, at around 3–5 years of age [64••] (but see [95]). The delayed peak can also be observed in peak aerobic glycolysis around the same period [96].

It was long suggested that a simple shift in life-history extending the infantile period could have aided rapid cultural accumulation across human generations, by allowing more time for learning [1,61,62,97]. The transcriptomic results imply that the early period of high synaptic plasticity, when learning is most rapid [93] (reviewed in [98–100]), was particularly extended. Human heterochrony is therefore not ubiquitous, but alters synaptic maturation in a specific brain region. Although enhancing learning in children, such heterochrony may also translate into synaptic activity and metabolism differences between adult humans and chimpanzees as observed earlier [20].

Bioinformatic analysis implicated myocyte enhancer factor 2A (*MEF2A*), a TF with roles in synaptic maturation and elimination, as the central regulator of human-specific delay in synaptic gene expression. Delayed expression of *MEF2A* in human PFC could then drive delayed synaptic maturation. Differential phosphorylation and sumoylation of *MEF2A* [101] between human and chimpanzee development could also contribute to downstream transcriptomic differences.

How is *MEF2A* mRNA abundance itself differentially regulated? As *MEF2A* regulation is activity-dependent [101,102], social/environmental differences between species could be responsible. Other possibilities include (perhaps prenatal) *trans* effects influencing *MEF2A*, or *cis* effects in *MEF2A*'s own regulatory sequence. An interesting finding here was a putative signature of recent positive selection upstream of *MEF2A*, dating after the split with Neanderthals [64••]. Although tentative, this result implies that delayed *MEF2A* signaling may be *cis* driven and that delayed synaptogenesis arose late in human evolution [103]. If delayed synaptic maturation also extended the vulnerable phase in human infancy, such delay might have only recently been possible, after sufficient technological advance [104].

human brain development. It thus contradicts the notion of conserved postnatal brain development among primates. This could have three explanations: (a) human-specific sequence changes mainly modify prenatal development [70], not yet directly compared between humans and chimpanzees; (b) remodeling involves numerous *cis* changes that fine-tune *trans* changes of large effect, and fine tunings are not detectable using current technology; (c) constraints on human brain development are relaxed. Distinguishing among these possibilities is a forthcoming challenge.

Future prospects

Transcriptome comparisons hitherto provided insight into general evolutionary processes and specific adaptive mechanisms shaping human brain evolution. One is the apparent predominance of negative selection and neutral changes in shaping adult species differences in mRNA abundance. Another is the role of heterochrony shaping specific processes (Box 2). Still, these are yet preliminary steps in understanding the genetic basis of human-specific cognitive phenotypes.

One way forward is studying under-investigated brain regions like the hippocampus or temporal cortex. Given that many adult expression differences simply reflect cell type composition differences, another approach could be cell type-specific [73] or single cell profiling. But the most promising endeavor might be focusing on comparative development and extending into the prenatal period. Although access to fetal tissue poses an obstacle, this can be partly overcome through comparative testing of human-specific *cis* changes for heterochronic action in mouse models (e.g. [74,75]), or studying human and chimpanzee development at the transcriptome level using organoids [9].

Finally, developmental mechanisms of human-specific phenotypic changes, such as delayed brain development, could also be in play in distant taxa. For instance, it was suggested that dogs have neotenous characters compared to wolves [76], while social insects may have neotenous brains compared to other insects [77]. Meta-analyses of brain development mechanisms across diverse social taxa could be another worthwhile strategy in understanding human evolution.

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